Relationship between drugs affecting the renin-angiotensin system and colorectal cancer: The MCC-Spain study

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Relationship between drugs affecting the Renin-angiotensin system and colorectal cancer: the MCC-Spain study

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ABSTRACT

The potential protective effect of Renin–angiotensin system (RAS) inhibitors is a subject of increasing interest due to their possible role as chemopreventive agents against colorectal cancer (CRC). To evaluate this association, we conducted a case-control study with 2,165 cases of colorectal cancer, diagnosed between 2007 and 2012, and 3,912 population controls frequency matched (by age, sex and region) from the Spanish multicenter case-control study MCC-Spain. We found a significant protective effect of the Angiotensin-converting enzyme Inhibitors (ACEIs) against CRC, limited to the under-65 years group (OR=0.65 95%CI (0.48-0.89)) and to a lesser degree to men (OR=0.81 95%CI (0.66-0.99). In contrast, the angiotensin receptor blockers (ARBs) did not show a significant effect. Regarding the duration of use, a greater protection was observed in men as the length of consumption increases. In contrast, in the under-65 stratum, the strongest association was found in short-term treatments. Finally, by analyzing ACEIs effect by colon subsite, we found no differences, except for under 65 years old, where the maximum protection was seen in the proximal intestine, descending in the distal and rectum (without statistical significance). In conclusion, our study shows a protective effect on CRC of the ACEIs limited to males and people under 65 years old, which increases in proximal colon in the latter. If confirmed, these results may suggest a novel approach to proximal CRC prevention, given the shortcomings of colonoscopy screening in this location.

Keywords: Colorectal cancer, Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker

INTRODUCTION

Colorectal cancer (CRC) is one of the most common forms of cancer worldwide with approximately 450,000 new cases detected in Europe in 2012 [1, 2]. In the last decades, the field of chemoprevention has experimented a rising interest, with the use of certain drugs to reduce the individual risk of cancer. Nowadays, the role of aspirin therapy in the reduction of colorectal cancer risk and precancerous adenomas [3, 4] is well known and there is increasing evidence of the chemopreventive effect of many others drugs used for cardiovascular diseases such as statins [5] and renin-angiotensin system (RAS) inhibitors [6]. In addition, recent observational studies and one meta-analysis have shown a protective effect of RAS therapy against CRC [7- 10]. Despite these encouraging findings, other studies have yielded conflicting results [11-13], calling for additional studies before recommending the clinical use of RAS inhibitors for CRC chemoprevention. The mechanism of action of the RAS-inhibitors combines both pro and antitumor effects, probably explain the controversial results obtained in observational studies. Moreover, the potential interaction with lifestyle factors (eg, diet) warrants more investigation [14]. Finally, it is important to identify whether there is a differential effect regarding the tumor anatomic subsite, given that, to the best of our knowledge, no previous studies have analyzed these aspects.

Therefore, the purpose of this work is to evaluate the effects of Angiotensin-converting-enzyme inhibitors (ACEis) and Angiotensin receptor blockers (ARBs) on overall colorectal cancer risk, and on its different anatomic locations, in a large population-based case-control study conducted in Spain, the MCC-Spain study.

MATERIALS AND METHODS

Study design and population

We conducted a multi-region case-control study “the Spanish multicase-control study” (MCC-Spain). This study was designed with the main objective of investigating lifetime environmental, infectious, medical and occupational exposures, as well as genetic factors associated with five cancer sites. Briefly, the MCC-Spain is a population-based case-control study of common tumors in Spain; the recruitment includes histologically confirmed incident cases of colorectal cancer diagnosed between January 1st, 2007 and March 31st, 2012. The cases were enrolled in 23 hospitals and primary care centers in 12 Spanish provinces together with a common set of matched population controls. Controls with no prior history of CRC

cancer were randomly selected from lists of primary care centers, according to age, sex and regional distribution of the cases included in the study. Response rates were 68% for colon cancer cases and 53% for controls, with no differences in the main socio-demographic variables among those who participated and those who refused to participate. The Ethics Committees of participating hospitals approved the study protocols, and participants provided written informed consent at the time of their inclusion in the study. Detailed clinical information was collected for all cases. The questionnaire is available on the website of the study (www.mccspain.org). Further information can be found elsewhere [15]. In the present study, we have selected only the 2,165 colorectal cancer cases recruited in MCC-Spain and their 3,912 frequency matched controls.

Data collection

Participants were interviewed face-to-face by trained monitors with a comprehensive epidemiological questionnaire that assessed socio-demographic information, personal and family history of cancer, anthropometric data, lifestyle, environmental exposure and medical history of medication/drugs use. To allow for a minimum latency period, all potential confounders that could be modified by the disease (tobacco and alcohol consumption, diet) were censored to 1 year prior to the interview. Regarding the life style, diet (including alcohol intake) was assessed with the use of a validated semi-quantitative Spanish Food Frequency Questionnaire (FFQ), which was modified to include regional products. The FFQ included 140 food items, and assessed usual dietary intake during the previous year.

Drug use assessment

Drugs use was recorded by indication. For each drug, the brand name, dose and duration of exposure were recorded to identify patients with regular drug consumption (“no and occasionally” versus “yes”) and the duration of consumption (more or less than 5 years). The drugs were coded by following the Anatomical Therapeutic Chemical Classification System (ATC codes) to define groups with similar mechanisms of action [16]. The ATC code included in the present analysis is code C09 (Agents acting on the renin-angiotensin system). We performed the analyses for ACEis drugs and for ARBs. For each of these analyses, we had as reference never having used the drug in question. We analyzed separately each colon subsite:

proximal colon (including cecum, ascending colon, transverse and hepatic and splenic flexures), distal colon (including descending colon, sigmoid and recto-sigmoid junction) and rectum. Anatomic subsites were defined according to Li et al [17].

Statistical Methods

Unconditional logistic regression was used to assess the association between treatment of ACEis and RAS inhibitors and colorectal cancer risk. To estimate the magnitude of the associations, multivariate-adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated. Multinomial logistic regression was used to assess the association between treatment of ACEis and ARBs and colorectal cancer subsites. All models included sex, age, province of recruitment (Asturias, Barcelona, Cantabria, Granada, Guipuzcoa, Huelva,Leon, Madrid, Murcia, Navarra and Valencia), educational level (less than primary school, primary school, secondary school, university), family history of colorectal cancer (no, first degree relatives, second degree relatives, others), smoking status one year before recruitment (never; former; current), alcohol consumption in the past (at 30-40 years old, in gms/day) and red meat (gms/day) and fruit and vegetable (gms/day) intake one year before the diagnosis in cases and the recruitment in controls, as potential confounders. A global 5% significance level was used for these analyses and all reported p-values are two-tailed. The exposure to the RAS inhibitors was analyzed globally and separately by duration of treatment (less than or equal to 5 years, or more than 5 years). Interactions were explored by including in the model the multiplicative interaction terms use/no use and sex (male/female), age (<65/≥65 years) or BMI (<25 Kg/m^2/ ≥25 Kg/m^2) respectively. Analyses were performed using the package Stata 14/SE (StataCorp, College Station, Tx, US).

RESULTS

During the study period, data from 2,165 colorectal cancer cases and 3,912 population controls were collected. The characteristics of cases and controls are shown in Table 1. The main differences between cases and controls were found at educational level, family history of colon cancer and diet. Controls had higher educational level and less often had a first-degree relative with colorectal cancer. Finally, regarding eating habits, controls had lower ethanol, energy and red meat intake and higher intake of vegetable.

RAS inhibitors and colorectal cancer

The use of ACEis showed a weak protective effect with borderline significance (OR=0.89, 95% CI (0.75-1.04)), while no association was observed with the ARB therapy (OR=1.00, 95% CI (0.73-1.19). A statistically significant interaction was seen between ACEis users and age, where the observed protection was restricted to the under 65 years old group (OR under-65=0.65; 95% CI (0.48-0.89) vs OR over-65=1.02 95% CI (0.84-1.24); p for ACEis-age interaction=0.03), and between ACEis and sex, where only men were protected (OR men=0.81; 95% CI (0.66-0.99) vs OR women=1.03 95% CI (0.78-1.37); p for ACEis-sex interaction=0.03). No changes were observed when stratifying by BMI (OR=0.85; 95% CI (0.61-1.19) vs OR=0.90 95% CI (0.75-1.09); p for ACEis-BMI interaction = 0.68) (Table 2).

Finally, considering the influence of length of consumption (Table 3), an opposite (regarding the length of consumption) effect was observed in men and in the under-65 group. While in the men group, long-term treatments presented the greatest protection (OR=0.71 95% CI (0.53-0.95) vs OR=0.91 95%CI (0.71-1.17)), in the under-65 group this effect is observed, instead, in short-term treatments (OR= 0.52 95%CI (0.34-0.77)). Stratifying by sex and age simultaneously (data not shown), the stronger association was observed in the group of men under 65 years old where the ACEis show a protective effect in short (OR= 0.55 95%CI (0.35-0.87)) but not long-term treatments (OR= 0.77 95%CI 0.43-1.40)). On the other hand, in the group of men over 65 years old, only the length of consumption greater than five years showed a protective effect (OR= 0.70 95%CI (0.50-0.99)).

RAS inhibitors and colorectal cancer subsite

To explore in more detail the potential association between the ACEis and ARBs and colon cancer we performed a subanalysis based on the location of neoplastic lesions.
The protective effect of the ACEIs was observed exclusively in the under 65 years subgroup, and was limited to the proximal (OR=0.50 95%CI (0.27-0.92)) and distal colon (OR=0.61 95%CI (0.39-0.95) (table 4). This protective benefit of ACEis was less pronounced in men and reached only borderline significance (OR=0.73 95%CI (0.51-1.02) in proximal vs OR=0.80 95%CI (0.61-1.05) in distal colon). Finally, when stratified by BMI, no significant effect was found. No relationship was observed between treatment with ARBs and colon cancer subsite, neither in the overall analysis, nor in the stratified analysis by sex, age and BMI factors (Table 5).

DISCUSSION

In this study, we analyzed a population-based case control study for evaluating the potential effect of RAS inhibitors on CRC. Our study shows a relevant protective effect against CRC for the ACEis limited to the under-65 group and to men, but no effect for the ARBs. The stronger association was observed in the under 65-year men where the ACEis show a protective effect in short term treatments. However, in men over 65, only the length of consumption greater than five years showed a protective effect.

Up to now, existing data regarding the effect of ACEis/ARBs on overall cancer risk are contradictory [18-21]. Randomized trials exploring this association usually have follow-up of less than five years, insufficient to detect cancer development. Moreover, they focus on cardiovascular outcomes as predefined clinical endpoints, being the cancer risk a 'post-hoc' analysis, thus possibly underreported. For these reasons, we limit our discussion to observational studies specifically designed to evaluate cancer. Most of the studies published in the last 5 years focusing on CRC have shown that the use of ACEis alone or combined with ARBs is associated with a decrease in the risk of CRC development [6, 7, 9], as well as in advanced adenomatous colon polyps [8] or advanced neoplasia. In addition, a recently published meta-analysis of observational studies [10] also found a protective effect of the combination of ACEis or ARBs against CRC. Regarding overall ACEis effect, we found a similar protection to that found in other studies combining ACEis and ARBs in their analyses [9, 10], but our results found only borderline significance. It is remarkable that this protection increased substantially in the under 65-year age group and less markedly in men. The influence of sex on colon cancer incidence is widely known and these differences increase progressively across the colon from the cecum to the rectum. Men have higher rates of CRC than women, probably due to sex-specific exposure to risk factors, differences in screening experiences and access to medical care and protective effects of both endogenous and exogenous hormones [22, 23]. In addition, the differential expression of estrogen receptors between the colonic subsites might explain the right-sided predominance of the neoplasm in women, even though the etiological role of these receptors is not yet well understood [24, 25]. Some studies suggest that, over time, the effectiveness of ACE inhibition is diminished in women [26]. These differences could be due to a modulatory effect of the sexual steroids on the expression and activity of the various components of the RAS, which would explain why the protective effect of ACEis was observed only in males in our study [27]. Regarding age differences, a gradual increase in the ratios of proximal-to-distal CRC with advancing age has been observed [28-30].

Finally, two recent meta-analyses have shown the influence of obesity and excess weight on the risk of developing CRC [31, 32]. Although most of the studies that have conducted analyses by CRC subsite have found a significant association between body size and distal adenomas or cancer, to date, evidence is still inconsistent [33].

Regarding the exposure time, we observed that the protective effect increased in long-term treatment (>5 years) only in men, while in the under-65 subgroup the protective effect was seen only in treatments lasting less than five years. However, the number of cases and controls under-65 exposed to ACEIs for more than five years was rather scarce, which makes it difficult to identify a length of treatment – effect relationship. Makar et al [9], also in a case-control study, found a clear association between long-term or high dose of RAS inhibitors and CRC protection.

On the other hand, the lack of association between ARBs therapy and CRC is consistent with others studies [11, 34, 35], which also studied separately the effect of ARBs. In contrast, Azoulay et al [7], in a case-control study nested in a cohort, found a weak, but significant protection (OR=0.90 95% CI (0.83–0.98)). Focusing on colorectal carcinogenesis, one experimental study [36] has demonstrated a beneficial effect of ACEi or ARB therapy reducing the total number of colonic premalignant lesions in obese mice. The role of angiotensin II in cell proliferation, cell migration, and angiogenesis suggests their participation in certain steps of tumor genesis and progression [37], and could explain the antitumor effect of the RAS inhibitors (inhibiting tumor angiogenesis, inducing cancer cell apoptosis and disrupting the microenvironment of tumor) [38, 39]. However, the mechanisms of action of the two types of RAS drugs, ACEis and ARBs, are quite different. While ACEis act inhibiting the conversion of angiotensin I to angiotensin II, ARBs act on the receptors of this hormone. The protective effect of ACEis has been demonstrated in animal models of solid cancers [40, 41], but certain authors have also found that the chronic treatment with ACEis might produce the accumulation of some peptides with protumor effect, such as bradykinin, substance P, and N-acetyl-seryl-aspartyl-lysyl-proline [42]. ARBs, in turn, selectively block the angiotensin II type 1 receptors, responsible for vasoconstriction, cell growth, and sympathetic activation and in this way exerts their potential antineoplastic effect, maintaining the beneficial effects of angiotensin II type 2-receptor stimulation (vasodilatory and antiproliferative action mediated via the kinin system) [21, 37]. Nevertheless, some studies have suggested a pro-tumoral effect of the ARBs as a result of the stimulation of free angiotensin II type 2-receptor, which results in increased tumor progression [18, 43, 44].

In the last decades, diverse reports have suggested that CRC is a heterogeneous disease [45]. At first, distinguishing two distinct categories of CRC, proximal and distal, was proposed. Thereafter rectal cancer, which is usually discussed together with colon cancer, was addressed specifically as another type of CRC [16]. This is the reason why we have analyzed separately the effect of RAS inhibitors according to the colon subsite. Our results show that the protective effect observed for ACEis did not reach statistical significance in the analysis by location. In the same way, ARBs did not show effect in any of the three locations. However, in the under-65 group, ACEis showed a lower protective effect as one progresses through the large intestine. Thus, maximum protection was seen in the proximal intestine, descending in the distal intestine and rectum, in this last case without statistical significance. In the same way, Kedika et al reported a statistically significant decrease in right sided polyps in ACE-I users. The fact that young people are less susceptible to developing right-sided colon cancer [23] suggests a synergistic interaction between ACEis and age.

To the best of our knowledge, this is the first study separately addressing the influence of the RAS inhibitors on CRC by colon location. It has been speculated that the risk factors for CRC may vary according to their anatomic location, because these structures arise from different embryonic tissue (the proximal colon from midgut and distal and rectum from hindgut) and serve different functions [45, 46].

Strengths and limitations

The strengths of this case-control study include, first, the enrollment of newly diagnosed colorectal cancer cases, verified with revision of the medical record and the pathological anatomy report, and population controls. Furthermore, all the information has been collected by personal interviews identically for cases and controls. This strategy allows us to control the principal confounding factors in the relation of RAS inhibitors and colorectal cancer (such as family history of colorectal cancer, smoke status, alcohol consumption, age or BMI) and include these variables in the adjusted analyses. Notwithstanding these strengths, our study has several limitations. First, we used self-reported drug use whereas most studies use pharmacy records or prescribing information. Although the validity of self-reported medication use has not been assessed in our study, other studies comparing self-reported use of antihypertensive medications with pharmacy databases [47] or physician reports [48] have showed that self-report is reasonably valid (sensitivity and specificity both being about 90%). Second, we were unable to explore a possible association between specific types of drugs previously associated with cancer (e.g. Lisinopril, Captopril, Losartan, Candesartan or Telmisartan), due to the small number of exposed in our study. Third, unfortunately, we could

not explore a dose-response effect of the drugs studied due to the poor quality of these data. Therefore, to approach the intensity of the relationship we have chosen to use the duration of treatment, considering more exposed those that took the treatment for more than 5 years.

CONCLUSIONS

Our study found a protective effect on the CRC risk of the ACEis limited to the under-65 group and less markedly in men. In those aged under 65 years, this protection shows a descending gradient across the colon and disappears in the rectum. Age and sex were modifiers of this association. We found no evidence of any effect on colorectal cancer risk among those exposed to the ARBs.

The potential protective effect of RAS inhibitors is a subject of increasing interest due to their possible role as chemopreventive agents against CRC [6, 14], but to date, there are still few studies that address this relationship. Further work is required to confirm these results, but our findings could represent a promising progress in CRC prevention, given the poorer results obtained with colonoscopy screening in proximal colon.

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ETHICAL APPROVAL

The study was carried out according to Spanish laws on biomedical research. The ethics committees of participant hospitals approved the protocol. Informed consent was obtained from all individual participants included in the study. All procedures were performed with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Table 1. Characteristics of the Colorectal Cancer Patients and Population-Based Controls

Variable	Category	Cases[1]	Controls
Age, mean±sd		67.0±10.8	63.3±11.8
Sex, n (%)	Men	1383 (63.9)	1995 (51.0)
	Women	782 (36.1)	1917 (49.0)
Geographical area, n (%)	Asturias	77 (3.6)	227 (5.8)
	Barcelona	698 (32.2)	996 (25.5)
	Cantabria	151 (7.0)	355 (9.1)
	Granada	166(7.7)	186 (4.8)
	Guipuzcoa	119 (5.5)	352 (9.0)
	Huelva	74 (3.4)	174 (4.5)
	Leon	405 (11.3)	440 (11.3)
	Madrid	233 (10.8)	726 (18.6)
	Murcia	36 (1.7)	42 (1.1)
	Navarra	125 (5.8)	266 (6.8)
	Valencia	81 (3.8)	148 (3.8)
Family history of colon cancer, n (%)	No	1679 (79.4)	3487 (88.8)
	First-degree relative	359 (17.0)	331 (8.4)
	Second-degree relative	78 (3.7)	110 (2.8)
Educational level, n (%)	Less than primary school	695 (32.1)	740 (18.9)
	Primary school	826 (38.2)	1273 (32.6)
	Secondary school	430 (19.9)	1109 (28.4)
	University	214 (9.9)	790 (20.2)
Tobacco smoking, n (%)	Never smoker	893 (41.3)	1739 (44.5)
	Former smoker	999 (46.1)	1420 (36.3)
	Current smoker	273 (12.6)	753 (19.3)
Body Mass Index (kg/m^2), n (%)	<18.5	20 (0.9)	48 (1.2)
	18.5-24.9	650 (30.0)	1420 (36.3)
	25.0-29.9	960 (44.3)	1620 (41.4)
	≥30	535 (24.7)	824 (21.1)
Energy intake (kcal/day), mean±sd		2008.4±708.2	1893±637.6
Ethanol intake (g/day), mean±sd		23.9±34.6	17.1±26.8
Red meat intake (g/day), mean±sd		34.7±28.6	29.5±23.4
Fruit intake (g/day), mean±sd		343.5±205.3	347.5±218.5
Vegetable intake (g/day), mean±sd		174.8±113.2	189±123.4

[1]All cases were diagnosed between 2007 and 2012.

Table 2. Relationship between Renin–angiotensin system inhibitors and colorectal cancer

Antihypertensive drug	Population	Unexposed controls / cases (n)	Exposed controls/ cases (n)	OR (95% CI)
Angiotensin-converting-enzyme inhibitors	All cases[1] and controls	3389/1842	523/323	0.89 (0.75-1.04)
	Men	1649/1171	346/212	0.81 (0.66-0.99)
	Women	1740/671	177/111	1.03 (0.78-1.37)
	<65 years,	1735/770	173/76	0.65 (0.48-0.89)
	≥65 years	1654/1072	350/247	1.02 (0.84-1.24)
	BMI<25Kg/m^2	1329/597	139/73	0.85 (0.61-1.19)
	BMI≥25Kg/m^2	2060/1245	384/250	0.90 (0.75-1.09)
Angiotensin receptor blockers	All cases[1] and controls	3523/1904	389/261	1.00 (0.73-1.19)
	Men	1744/1222	251/161	0.88 (0.70-1.10)
	Women	1779/682	138/100	1.29 (0.96-1.75)
	<65 years	1804/785	104/61	0.89 (0.62-1.27)
	≥65 years	1719/1119	285/200	1.04 (0.84-1.29)
	BMI<25Kg/m^2	1400/620	68/50	1.30 (0.86-1.95)
	BMI≥25Kg/m^2	2123/1284	321/211	0.94 (0.77-1.16)

OR: Odds ratio adjusted for age, recruitment area, education level, tobacco smoking history, BMI, family history of colorectal cancer, Ethanol intake (g/day) Red meat intake (g/day), Fruit intake (g/day), Vegetable intake (g/day), CI: confidence interval

[1]All cases were diagnosed between 2007 and 2012.

Table 3. Relationship between Renin–angiotensin system inhibitors consumption and colorectal cancer, according to length of consumption

Antihypertensive drug	Population	No consumption Controls/cases (n)	Consumption≤5y Controls/cases (n)	OR (95% CI)	Consumption>5y Controls/cases (n)	OR (95% CI)
Angiotensin-converting-enzyme inhibitors	All cases[1] and controls	3389/1842	275/171	0.90 (0.72-1.11)	248/152	0.88 (0.70-1.11)
	Men	1649/1171	184/127	0.91 (0.71-1.17)	162/85	0.71 (0.53-0.95)
	Women	1740/671	91/44	0.89 (0.59-1.34)	86/67	1.18 (0.82-1.69)
	<65 years	1735/770	111/41	0.52 (0.34-0.77)	62/35	0.91 (0.57-1.45)
	≥65 years	1654/1072	164/130	1.16 (0.89-1.51)	186/117	0.91 (0.70-1.18)
	BMI<25Kg/m^2	1329/597	76/48	0.99 (0.65-1.50)	63/25	0.69(0.41- 1.14)
	BMI≥25Kg/m^2	2060/1245	199/123	0.86 (0.67-1.11)	185/127	0.95 (0.74 1.23)
Angiotensin receptor blockers	All cases[1] and controls	3523/1904	222/153	1.02 (0.82-1.29)	167/108	0.88 (0.70-1.11)
	Men	1744/1222	144/99	0.95 (0.72-1.27)	107/62	0.77 (0.54-1.08)
	Women	1779/682	78/54	1.18 (0.80-1.74)	60/46	1.45 (0.94-2.25)
	<65 years	1804/785	59/40	0.92 (0.59-1.44)	45/21	0.82 (0.46-1.44)
	≥65 years	1719/1119	163/113	1.05 (0.80-1.38)	122/87	1.02 (0.74-1.39)
	BMI<25Kg/m^2	1400/620	42/33	1.35 (0.82-2.22)	26/17	1.21 (0.62-2.3)
	BMI≥25Kg/m^2	2123/1284	180/120	0.96 (0.74-1.24)	141/91	0.92 (0.68-1.23)

OR: Odds ratio adjusted for age, recruitment area, education level, tobacco smoking history, BMI, family history of colorectal cancer,. Ethanol intake (g/day) Red meat intake (g/day), Fruit intake (g/day), Vegetable intake (g/day), CI: confidence interval

[1]All cases were diagnosed between 2007 and 2012.

Table 4. Relationship between Angiotensin-converting-enzyme inhibitors and colon cancer by location

Population	Cancer type	Unexposed controls /cases (n)	Exposed controls/cases (n)	OR (95% CI)
All cases[1] and controls	Proximal colon	3385/488	523/85	0.87 (0.67-1.13)
	Distal colon	3385/749	523/126	0.83 (0.66-1.03)
	Rectal cancer	3385/562	523/106	1.00 (0.79-1.27)
Men	Proximal colon	1649/288	346/46	0.73 (0.51-1.02)
	Distal colon	1649/469	346/88	0.80 (0.61-1.05)
	Rectal cancer	1649/382	346/74	0.92 (0.69-1.17)
Women	Proximal colon	1740/200	177/39	1.15 (0.76-1.72)
	Distal colon	1740/280	177/38	0.87 (0.58-1.29)
	Rectal cancer	1740/180	177/32	1.18(0.76-1.83)
<65 years	Proximal colon	1735/182	173/13	0.50 (0.27-0.92)
	Distal colon	1735/302	173/29	0.61(0.39-0.95)
	Rectal cancer	1735/274	173/32	0.77 (0.50-1.20)
≥65 years	Proximal colon	1654/306	350/72	1.04(0.77-1.39)
	Distal colon	1654/447	350/97	0.96(0.74-1.25)
	Rectal cancer	1654/288	350/74	1.15 (0.86-1.55)
BMI<25Kg/m^2	Proximal colon	1329/151	139/17	0.81 (0.46-1.42)
	Distal colon	1329/232	139/24	0.67 (0.41- 1.09)
	Rectal cancer	1329/203	139/30	1.10 (0.70-1.75)
BMI≥25Kg/m^2	Proximal colon	2060/337	384/68	0.89 (0.67-1.20)
	Distal colon	2060/517	384/102	0.88 (0.68-1.13)
	Rectal cancer	2060/359	384/76	0.95 (0.72-1.27)

OR: Odds ratio adjusted for age, recruitment area, education level, tobacco smoking history, BMI, family history of colorectal cancer, Ethanol intake (g/day) Red meat intake (g/day), Fruit intake (g/day), Vegetable intake (g/day), CI: confidence interval

[1]All cases were diagnosed between 2007 and 2012.

Table 5. Relationship between Angiotensin receptor blockers and colon cancer by location

Population	Cancer type	Unexposed controls / cases (n)	Exposed controls/cases (n)	OR (95% CI)
All cases[1] and controls	Proximal colon	3523/491	389/82	1.17 (0.89-1.53)
	Distal colon	3523/765	389/110	1.02 (0.81-1.30)
	Rectal cancer	3523/603	389/65	0.86(0.64-1.15)
Men	Proximal colon	1744/288	251/46	1.04 (0.73-1.49)
	Distal colon	1744/487	251/70	0.91 (0.67-1.23)
	Rectal cancer	1744/414	251/42	0.76 (0.53-1.09)
Women	Proximal colon	1779/203	138/36	1.39 (0.91-2.12)
	Distal colon	1779/278	138/40	1.31 (0.88-1.96)
	Rectal cancer	1779/189	138/23	1.17(0.71-1.93)
<65 years	Proximal colon	1804/180	104/15	0.91 (0.50-1.66)
	Distal colon	1804/301	104/30	1.18(0.75-1.85)
	Rectal cancer	1804/290	104/16	0.64 (0.36-1.13)
≥65 years	Proximal colon	1719/311	285/67	1.27 (0.93-1.73)
	Distal colon	1719/464	285/80	0.98(0.74-1.30)
	Rectal cancer	1719/313	285/49	0.96 (0.68-1.35)
BMI < 25Kg/m^2	Proximal colon	1400/157	68/11	0.96 (0.48-1.91)
	Distal colon	1400/232	68/24	1.64 (0.98- 2.75)
	Rectal cancer	1400/218	68/15	1.26 (0.68-2.34)
BMI≥25Kg/m^2	Proximal colon	2123/334	321/71	1.21 (0.90-1.62)
	Distal colon	2123/533	321/86	0.92 (0.70-1.20)
	Rectal cancer	2123/385	321/50	0.79 (0.56-1.10)

OR: Odds ratio adjusted for age, recruitment area, education level, tobacco smoking history, BMI, family history of colorectal cancer,. Ethanol intake (g/day) Red meat intake (g/day), Fruit intake (g/day), Vegetable intake (g/day), CI: confidence interval

[1]All cases were diagnosed between 2007 and 2012.

Highlights

- Angiotensin-converting enzyme inhibitors protect against colorectal cancer.
- This effect is limited to males and people under 65 years old.
- The stronger association is observed in proximal colon.